REMARKS

1.0 Status of the claims:

Claims 1-4, 7-12 and 16-25 are pending and ready for further action on the merits.

Claims 1-4, 7-12, and 16-25 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

2.0 Rejections under 35 U.S.C. § 112, first paragraph

Claim 1-4, 7-12, and 16-25 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for claiming solvates of the compounds of the instantly claimed invention.

Applicants traverse.

3.0 Response to Examiner's arguments

Applicants remind the Examiner that the standard for determining whether a claim is enabled is whether one can practice the claimed invention without undue experimentation. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The *Wands* factors are factors that are to be considered to determine whether a claim is enabled. No one *Wands* factor can be used by itself to assert that a claim is not enabled. Rather, it is the totality of the *Wands* factors that determine whether a claim is enabled or not.

Moreover, the initial burden is on the Examiner to present evidence asserting why the claims are not enabled. In *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971), the court stated, "it is incumbent upon the Patent Office, whenever a rejection on this [enablement] basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

With the above in mind, Applicants assert that solvates are enabled. Applicants have gone through the *Wands* factors in previous responses and explained in detail why

the claims are enabled for solvates. Applicants in this response address the Examiner's assertions from the Office Action mailed January 26, 2009 and again explain why solvates are enabled. Moreover, Applicants provide additional evidence that solvates are enabled.

On page 6 of the January 26, 2009 Office Action, the Examiner states that "The experimentation for solvates is potentially open-ended." Applicants disagree. Applicants have provided references that demonstrate that the formation of solvates is routine including the *Ex Parte Gante* Board decision (Appeal No. 2000-0600 (BPAI, 2002)). The Examiner dismisses *Gante* because the cited statements appear in a section where a 35 U.S.C. § 112, second paragraph, rejection was addressed. The key statement by the board in *Gante* was that the selection of appropriate solvents for formation of solvates was routine. Applicants submit that it does not matter whether the Board's statements were part of a definiteness analysis or an enablement analysis.

Moreover, the Examiner dismisses the *Gante* decision because the decision issued "years ago." The date of the *Gante* decision was May 6, 2002 and the date of publication of Vippagunta was 2001. The *Gante* decision issued after the publication of Vippagunta, which is the only literature reference cited by the Examiner in support of the Examiner's rejection of the pending claims for lack of enablement. Thus, *Gante* was not "years ago." Further, the *Gante* decision assessed the compliance with § 112, second paragraph, of an application that was filed May 3, 1996. If the selection of appropriate solvents for formation of solvates was routine at the time of the relevant application in *Gante* in 1996, it should be considered even more routine at the time the present application was filed in 2004.

Accordingly, Applicants do not understand how the Examiner can dismiss the statement of *Gante* as not being relevant to the enablement rejection in the present application. In *Gante*, the Board stated that the selection of solvents for the formation of solvates is routine. Moreover, the term solvate in the *Gante* application (US App. No. 08/642,268, now US 6,455,529) is used in a manner similar to the manner in which Applicants have used the term solvate in the present application. In light of *Gante*, Applicants respectfully request that the Examiner withdraw the enablement rejection.

On page 6 of the January 26, 2009 Office Action, the Examiner states that the specification merely mentions the Applicants' intention to make solvates, without teaching the preparation thereof. Applicants again point out that it is well settled law that one need not disclose, and preferably omits that which is well known in the art. Please note *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986) and a series of cases that hold similarly. See also *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984) as examples. Applicants have provided several references that state that the preparation of solvates is routine and have also provided references that explain how one would go about making solvates. In this response, Applicants provide additional references showing that the formation of solvates was known and routine in the art at the time of filing this application. The Examiner asserts that Applicants must show the preparation of solvates. This assertion is inapposite because methods for making solvates were well known and routine at the time that the present application was filed.

On page 7 of the January 26, 2009 Office Action, the Examiner states that no working examples are provided. The Examiner cites a passage from *Morton International Inc. v. Cardinal Chemical Co.*, 5 F.3d 1464 (Fed Cir. 1993) to support the proposition that because the specification shows no evidence of formation of or actual existence of solvates, Applicants must show formation of solvates or limit the claims accordingly.

There are at least two points that should be raised from the Examiner's reliance on *Morton*. First, *Morton* correctly describes that the initial burden of proof rests with the party asserting the claims are not enabled. In this regard, the court in *Morton* states:

> *The court correctly required Cardinal to prove by clear and convincing evidence facts establishing lack of enablement. (Id. at 1470)*

This passage correctly assigns the initial burden on the party asserting that the claims are not enabled. Similarly, and as described above regarding *Marzocchi*, the initial burden of proof rests with the Examiner to show why the claims are not enabled. Contrary to the Examiner's statement on page 11 of the January 26, 2009 Office Action that "evidence is given in the instant application which rebuts Applicant's argument that the preparation of

solvates is highly routine," Applicants submit that the Examiner has not provided any acceptable evidence or reasoning that solvates of the claimed compounds can only be made through undue experimentation.

Second, Applicants submit that the Examiner has ignored the facts in *Morton* and has taken the quote that appears in the January 26, 2009 Office Action out of context. A complete transcription of the passage in *Morton* is shown below with the text cited by the Examiner underlined.

> *The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However, the district court found that*
>
> *[e]ven with the aid of sophisticated analytical instrumentation and the use of model systems which attempt to provide the compounds claimed in the '881 patent, however, there is no evidence that such compounds exist.* ***The clear and convincing evidence has shown that the examples of the '881 patent do not produce the postulated compounds.*** *Rather, the examples and procedures produce a complex mixture of alkyltin mercaptides and alkyltin sulfides. The evidence established that a number of these are prior art compounds known to be useful as heat stabilizers.*
>
> *These findings are supported by the record. On review of the record,* ***there is considerable evidence showing that those skilled in the art could not make the claimed compounds using the procedures of the specification****, and no evidence that such compounds even exist. (emphasis added)*

Applicants direct the Examiner's attention to the two bold passages in the above quotation. "Clear and convincing" and "considerable" evidence was on the record that the examples of the patent at issue did not produce the claimed compounds. This is vastly different from the instant case where the Examiner has presented no acceptable evidence or reasoning that solvates of the presently claimed compounds can not be made through routine experimentation.

The one literature reference on which the Examiner does rely (i.e., Vippagunta) is ambiguous as to whether solvate formation is predictable or not. The Examiner in the Office Action mailed May 5, 2008 cites a passage on page 18 of Vippagunta, which states

> *Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult.*

The Examiner has used this passage to show that solvate formation is unpredictable. First, Applicants note that predictability is only one of the *Wands* factor to consider in determining whether the claims are enabled or not. Predictability, by itself, is not dispositive of enablement. Moreover, this statement from Vippagunta states nothing about whether this alleged unpredictability would make the experimentation required to generate solvates undue. Simply because something has some unpredictability, it does not mean it is not enabled.

Second, Vippagunta, in another passage, states:

> *The recent developments in computational chemistry allow the prediction of possible polymorphic forms based only on the molecular structure of the drug. The Polymorph Predictor, from Molecular Simulations, is currently the only commercial software package that can predict the possible polymorphs of an organic compound from its molecular structure. (See page 11, right hand column). . . This method has been successfully employed to generate known polymorphs of primidone . . .. and progesterone*

Applicants note that in this passage, Vippagunta has acknowledged that there is some predictability to deducing possible polymorphic structures if the molecular structure is known. Vippagunta also points out that there was commercial software available at least in 2001 that allowed one to predict the polymorphs that can be made if the structure was known. Applicants in the present case do know the molecular structures of the claimed compounds. Moreover, Vippagunta also discloses that the software package that has been used to predict the solvate structure in the formation of solvates of several compounds was known when the present application was filed. Thus, when Vippagunta is viewed as a whole, one can only come to the conclusion that Vippagunta acknowledges that there is some predictability to the formation of solvates.

On page 9 of the January 29, 2009 Office Action, the Examiner cites a passage from Souillac, et al., which states:

> *Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity from one form to another may be different. Studying the polymorphism of a drug*

> *and the relative stability of the different polymorphs is a critical part of pre-formulation development.*

and cites on page 8 a passage from *Smithkline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1348 (Fed. Cir. 2005), which states:

> *"Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) . . . [P]seudopolymorphs are often loosely called polymorphs . . . Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.*

The Examiner cites these passages to support the Examiner's conclusion that solvate formation is unpredictable. However, the cited passages have no probative value with regard to the issue of predictability of formation of solvates or even to the issue of the level of experimentation needed to prepare solvates. Instead, the passages cited by the Examiner deal with the physical characteristics of solvates such as therapeutic activity. Whether or not some differences of physical characteristics between solvates and other forms of the compounds of the present claims exist, such differences are irrelevant with respect to predictability of formation or the issue of the level of experimentation needed to prepare solvates.

Finally, the Examiner has not provided acceptable evidence or reasoning demonstrating why one should doubt the truth or accuracy of Applicants statements as required in *Marzocchi*. Accordingly, the Examiner has failed to shift the burden to Applicants as to why the claims are not enabled for solvates.

3.1 Methods of preparing solvates are routine and well known in the art

As discussed in the November 5, 2008 response, and as evidenced by the Caira reference (discussed again below), methods for preparing solvates are well known and routine in the art. Applicants below summarize four additional references that further establish the extensive knowledge available to one of skill in the art prior to the filing date of the present application.

3.1.1 The state of the art

3.1.1.1 Caira

Caira describes "[n]umerous examples of polymorphic systems . . . to illustrate the applications of both older and newer techniques for their [formation and] investigation . . . includ[ing] studies of pseudopolymorphism manifested by hydrates and solvates of the parent organic molecule." Caira at 164. Caira Section 3.1 (pages 177-180) provides also a review of methods of preparing polymorphs and pseudopolymorphs (i.e., solvates), and describes how characterization of polymorphs "normally commences with experimental screening [e.g., by hot stage microscopy] . . . to provide preliminary indications of the presence of crystalline polymorphic and pseudopolymorphic (solvated) . . . forms." *Id.* at 177. Applicants note that it is this exact screening that is described by Caira as routine in the pharmaceutical arts, yet the Examiner continues to assert that the screening for solvates requires undue experimentation. Caira also teaches that "[m]ost pseudopolymorphs are prepared by crystallization of the parent organic compound from the respective solvent, whereupon the latter becomes incorporated in the new crystal." *Id.* Caira further describes that "[e]xposure of the parent organic compound to vapours may also result in the formation of pseudopolymorphs (as occurs e.g. when anhydrous drugs react with atmospheric water to form hydrates)," and refers to the drug indomethacin as an example. *Id.* In other words, Caira not only informs one skilled in the art how to make solvates but also gives an actual example of Caira's method.

3.1.1.2 Vippagunta

Several passages from Vippagunta et al. were discussed above. Vippagunta et al., "Crystalline Solids", Advanced Drug Discovery Reviews, 48 (2001) 3-26 ("Vippagunta"), reviews recent advances in the prediction and characterization of polymorphs and solvates. Section 3, page 15, specifically addresses hydrates and solvates. Vippagunta cites Guillory, "Generation of polymorphs, hydrates, solvates, and amorphous solids", in H.G. Brittain, (Ed.), Polymorphism in Pharmaceutical Solids, vol. 95, Marcel Dekker, New York, 1999, pp. 183-226 ("Guillory", discussed below) as discussing the various methods of preparation of hydrates and solvates in detail.

Vippagunta does recognize, as discussed above, that predicting the formation of a particular solvate may not be straightforward. See Vippagunta, Section 3.4, p. 18. However, Applicants' claimed invention is not a method to predict solvates, but rather the claims relate to compounds of Formula I and pharmaceutically acceptable salts and their solvates. As discussed below, while the "level of predictability in the art" is one of the *Wands* factors, the level of predictability by itself is not dispositive of the question of enablement.

3.1.1.3 Guillory

Guillory describes methods employed to obtain solvated forms of compounds. Guillory is specifically written to teach how to make solvates and other solid state forms of pharmaceutical compounds:

Guillory, at page 186 states:

> *In this chapter, the various methods used to isolate polymorphs, hydrates, and solvates will be described. . . . In this context, it is hoped that the following information will prove useful in devising a "screening" protocol for the preparation of the various solid state forms of pharmaceuticals. While one cannot be absolutely certain that no additional forms will be identified in the future, this approach should provide some assurance that "due diligence" has been exercised to isolate and identify crystalline forms that are likely to arise during the normal course of drug development . . ..*

The methods employed to obtain hydrate forms and those employed to obtain solvate forms are described in sections II and III of Guillory, beginning at page 202. Guillory gives specific methods one of skill in the art can use to prepare hydrates and solvates. Guillory, a 1999 publication, is not directed to whether or not solvates might exist. Guillory infers that "due diligence", using methods known in the art, will confidently put one of ordinary skill in possession of the crystalline forms likely to arise in the normal course of drug development. This is not undue experimentation but deliberate research, within the level of ordinary skill. Guillory does not ask "what if" but sets out "how to" make solvated forms.

3.1.1.4 Byrn

Byrn, et al., Solid-State Chemistry of Drugs, 2nd Ed., 1999 SSCI, West Lafayette, IN, ("Byrn") contains its own chapter on "Hydrates and Solvates", chapter 11. Tables 11.1 and 11.2 both list numerous pharmaceutical solvates and hydrates. This chapter provides an extensive discussion of the formation of these compositions. One skilled in the art would have knowledge of the methods used to make these solvates.

3.1.1.5 Morissette

Morissette et al., "High-throughput crystallization: polymorphs, salts, co-crystals, and solvates of pharmaceutical solids", Advanced Drug Discovery Reviews 56 (2004) 275-300 ("Morissette ") provides a further perspective on screening for and preparing solvates. Applicants recognize that the Morissette publication date is after the priority date of the present invention but because Morissette is a review publication, almost all of the papers[1] referred to therein predate the filing date of the present invention. Morissette discloses high throughput methods from the perspective that "Exploration of a given compound's polymorphs, hydrates, solvates, salts, co-crystals and combinations of all of these appears intractable by conventional experimental methods, and the number of potential methods for exploring and controlling crystal form diversity continue to expand, existing strategies will become increasingly inadequate." Morissette, p. 278. While Morissette discloses the uses and advantages of high throughput methods to prepare and explore polymorphs, solvates, etc., it does so in view of the previously known and used prior art procedures. In other words, Morissette presumes one of skill in the art would know and have used these procedures and introduces yet another method.

Each of the above references, Caira, Vippagunta, Guillory, Byrn, and Morissette, are review articles. This fact should not be overlooked. As review articles, they describe and synthesize that which is known in the art. In other words, the prior art has more in it, and more available to one of ordinary skill, than simply the discussion of these review articles. Each of these review articles discusses specific examples and provides citations

[1] Twenty-one of the 113 papers and publications referred to in Morissette have publication dates in 2003. None of the references have publication dates in 2004 or later.

to the original articles. A review of the cited references in each of these review articles gives an idea of the information available to one of skill in this area.

In view of the state and teachings of the prior art, it is apparent that methods of making and characterizing solvates are routine and well known to one skilled in the art. Using methods such as those described in Caira, Vippagunta, Guillory, Byrn, or Morissette, it would require nothing more than routine experimentation to make the solvates claimed. The solvates of the present invention are sufficiently enabled. For this reason alone, Applicants request that the Examiner withdraw the enablement rejection of the pending claims.

3.2 Working examples are not required

With respect to the Examiner's assertion that the lack of working examples also supports a lack of enablement, courts have held that there is no requirement for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 422 F.2d 904, 951, 164 USPQ 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 USPQ 79 (Pat. Off. Bd. App. 1986). Given that one skilled in the art could make and identify various solvates of a particular organic molecule using the routine screening methods discussed above and below, no working example is necessary to enable the invention.

4.0 Applicants' additional arguments in support of enablement

4.1 Comparison of the present invention to that in *In re Wands*

Applicants direct the Examiner's attention to the similarities of the facts associated with the presently claimed invention to the facts in *Wands*. The issue in *Wands* was whether the patentee had adequately enabled one skilled in the art to make high-affinity IgM antibodies against HbsAg that were needed to practice the claimed assay methods. *See Wands*, 858 F.2d at 735. The PTO had rejected the method claims as not being enabled for the reason that the production of high-affinity IgM anti-HbsAg antibodies was unpredictable and unreliable, thus requiring undue experimentation. *Id.* However, the Federal Circuit reversed and made the point that even though screening for hybridomas was labor-intensive with numerous steps (*e.g.*, immunizing animals, fusing

lymphocytes from the immunized animals with myeloma cells, cloning the hybridoma, screening the resulting antibodies, etc.), all the methods needed to practice the invention were well known, and the amount of effort was not excessive enough to be undue despite any unpredictability associated with making antibodies. *See id.* at 740.

The court found that it would not require undue experimentation to obtain the monoclonal antibodies despite the extensive experimentation that was needed. The formation and characterization of solvates of a given organic molecule requires substantially less experimentation than preparing monoclonal antibodies because it is simpler, substantially easier, requires significantly fewer steps, and demands much less time than for the preparation of a monoclonal antibody. Accordingly, if the court in *Wands* concluded that the preparation of a monoclonal antibody was enabled despite the complex and lengthy process involved, it is unreasonable to reject solvates in this application as lacking enablement given that they are simpler to make. The table below provides a step-by-step comparison of some of the major steps involved in the production of a monoclonal antibody (as disclosed in *Wands*) and the fewer number of steps involved in making a solvate.

Table[2]

Step	Monoclonal Antibody	Hydrate or Solvate
1	Immunize animal	Expose the compound to solvent
2	Remove the spleen from the immunized animal	Remove any excess solvent and/or reducing the temperature, and possibly seeding for solid formation
3	Separate the lymphocytes from the other spleen cells	

[2] In addition to the steps described in the Table, there may be several other steps in the production of monoclonal antibodies not described in *Wands* (*e.g.*, preparation of antigen, repeated immunization of animals, testing of animal serum for the presence and titer of the antibodies of choice, introduction of hybridoma cells into animals to induce liquid ascytes tumors, draining the ascytes tumors from the living animals, purification of monoclonal antibodies from the ascytes fluid, etc.).

4	Mix the lymphocytes with myeloma cells	
5	Treat the mixture to cause fusion between the lymphocytes and the myeloma cells to make hybridomas that hopefully secrete the desired antibody	
6	Separate the hybridoma cells from the unfused lymphocytes and myeloma cells by culturing in a medium in which only hybridoma cells survive	
7	Culture single hybridoma cells (often 100 different cells) in separate chambers	
8	Assay the antibody secreted from each hybridoma culture to determine if it binds to the antigen	Assay isolated solid to determine if solvate has formed
Total Time	Months	Hours to days (depending on volatility of solvent)

As is shown in the above Table, the production of a monoclonal antibody is much more complex and time-consuming than the production of a solvate, yet the court in *Wands* concluded that it was not excessive and undue. Thus, to say that preparation of solvates in the claims of this application would require undue experimentation and, thus, are not enabled, while the monoclonal antibodies in *Wands* are enabled, is clearly inconsistent.

While the complexity of the procedures for making monoclonal antibodies and solvates is highly disparate, the processes share the characteristic that the step(s) involved are well known and routine. This is clearly shown by the review articles cited by Applicants above. To make solvates, samples of the organic compound are exposed to various different solvents. Once the solvates are formed, they can be readily analyzed by routine methods, including thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fischer titrimetry, X-ray diffractions (single crystal or powder), infrared spectroscopy (IR), polarized light microscopy, and hot stage microscopy or other routine techniques to detect and quantify the presence of hydrate or solvate molecules in the sample. *See, e.g.,* Vippagunta, at 18, right column.

Exposure of the organic compounds to various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from solvent. *See also* Caira

and Guillory as discussed above. While there may be many solvents and conditions to try, the screening of solvents for the ability to form solvates with a given organic compound merely uses methods that are well known in the art and considered quite simple. And, as explained by the court in *Wands*, "the test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *Wands* at 737. Applicants also note that there are numerous companies that offer to provide such screening services (usually combined with polymorph screens) and advertise how quickly and efficiently they can screen for solvates. Example companies offering these services include Wilmington PharmaTech (Newark, DE), Avantium Technologies (Amsterdam), and SSCI/Aptuit (West Lafayette, IN). As screening for solvates merely uses well known and routine methods, and the methods involved are simpler and easier to carry out than the steps for preparing monoclonal antibodies (*e.g.*, exposing a chemical sample to air versus immunizing an animal, followed by splenectomy, followed by lymphocyte isolation, followed by fusing lymphocytes with myeloma cells, followed by isolating hybridoma cells, etc.), the amount of experimentation cannot be considered excessive and undue.

The Examiner attempts to base the enablement rejection on (1) unpredictability of solvate formation and (2) lack of working examples. Unpredictability was the main reason for the PTO's rejection of the claims in *Wands*, yet the rejection was reversed by the Federal Circuit because all the methods needed to practice the invention were well known and the amount of effort was not undue, as mentioned above.

As in *Wands*, where the court concluded that methods for making monoclonal antibodies were enabled when the applicants showed that these antibodies can be made using hybridomas with well known methods, here, Applicants have shown that solvates can be easily made and characterized using routine well known methods. The court in *Wands* did not require a prediction of the specific primary or secondary sequence of the monoclonal antibodies, but was satisfied that all the methods needed to make the antibodies were well known.

Moreover, as was discussed above with regard to *Marzocchi,* the Examiner cites insufficient evidence to support a *prima facie* case of non-enablement. As explained above and in the Applicants' previous response, the methods of making and

characterizing solvates are well known, available, and routine. Accordingly, any unpredictability associated with solvate formation that might exist is clearly outweighed by the fact that preparing and screening for solvates is routine and employs well known methods.

4.2 Patents with similar claims to those of present application

After searching the PTO database of issued patents in a brief manner, the following U.S. Patents were readily identified as having claims reciting solvates, and as having no more description about how to make and use solvates then the presently claimed invention, and yet having no enablement rejections to the same: U.S. Patent Nos. 7,232,823; 7,230,024; 7,230,002; 7,229,991; 7,442,839; 7,476,674; 7,482,342; 7,485,660; 7,491,710; 7,491,733; and 7,491,742. Applicants see no difference between these patents and the present application with respect to enablement of solvates and, thus, believe that the enablement rejection in this application should be withdrawn.

5.0 Conclusion

The Examiner fails to provide any acceptable evidence or reasoning that the making and use of solvates is anything but routine in the pharmaceutical industry and far simpler than the manufacture and screening of the monoclonal antibodies that were at issue in *Wands*. The Examiner's absolute requirement for predictability of forming solvates with the claimed compounds is inappropriate under the reasonableness-based *Wands* analysis and the weight of the evidence provided by Applicants. Enablement is about being able to practice the invention without undue experimentation, not about predicting with 100% certainty the outcome of any experiment. Because preparation of solvates merely involves the use of well known methods and would not require excessive effort, and because patents are routinely issued containing solvate language without objection during prosecution, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, enablement be reconsidered and withdrawn.

6.0 Fees

Applicants herein petition for a three month extension fee. Applicants believe that no additional fee is necessary, however, should an additional fee be deemed to be necessary, the Commissioner is hereby authorized to charge any fees required by this action or any future action to Deposit Account No. 16-1435.

With the above remarks, Applicants believe that all objections and/or rejections have been obviated. Thus, each of the claims remaining in the application is in condition for immediate allowance. A passage of the instant invention to allowance is earnestly solicited.

Should the Examiner have any questions relating to the instant application, the Examiner is invited to telephone the undersigned at the below number to discuss any issues.

Respectfully submitted,

Date: July 16, 2009

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